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Review

Role of MAGI2-AS3 in malignant and non-malignant disorders

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ABSTRACT

MAGI2 Antisense RNA 3 (MAGI2-AS3) is a long non-coding RNA (lncRNA) transcribed from a locus on 7q21.11. This lncRNA has been described to be abnormally expressed in a variety of malignancies in correlation with many clinical characteristics. Moreover, it might participate in the pathogenesis of congenital diaphragmatic hernia, Alzheimer's disease and intervertebral disc degeneration. Mechanistically, MAGI2-AS3 can serve as a molecular sponge for miR-142-3p, miR-424-5p, miR-15b, miR-233, miR-452-5p, miR-629-5p, miR-25, miR-155, miR-23a-3p, miR-519c-3p, miR-374b-5p, miR-374a, miR-31-5p, miR-3163, miR-525-5p, miR-15-5p, miR-374a-5p, miR-374b-5p, miR-218-5p, miR-141-3p and miR-200a-3p to regulate expression of their mRNA targets. The current review summarizes the role of MAGI2-AS3 in different disorders to highlight its importance in their pathophysiology.

1. Introduction

Long non-coding RNAs (lncRNAs) are a group of RNA molecules that share numerous features with mRNAs but they lack substantial open reading frames, therefore they do not produce functional polypeptides except for rare cases [14–17]. Being acknowledged as a new group of epigenetic regulators, lncRNAs regulate epigenetic modifications principally in the nucleus, and influence transcription of genes through modulation of histone or DNA modifications [46]. Recently, expression and function of several lncRNAs have been assessed in different contexts revealing their contributions in several aspects of cell physiology, particularly regulation of activity of signaling pathways [9,24].

MAGI2 Antisense RNA 3 (MAGI2-AS3) is an lncRNA being transcribed from a locus on 7q21.11 (Fig. 1). This lncRNA has been reported to be aberrantly expressed in a variety of malignancies in correlation with many clinical characteristics [40]. At least 48 transcripts have been identified for MAGI2-AS3 (https://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000234456;r=7:79452877-79471208). This lncRNA is mainly expressed in the nucleus and within in extracellular compartments where it has low expression level [40]. Moreover, GeneCard online database (https://www.genecards.org) has shown high level of MAGI2-AS3 in the thyroid, heart, and kidney [40]. Abnormal expression of MAGI2-AS3 has been spotted in a variety of tumors as well as some non-malignant conditions congenital diaphragmatic hernia, Alzheimer's disease and intervertebral disc degeneration. The current review summarizes the role of MAGI2-AS3 in these conditions.

2. Malignant disorders

2.1. Cell line studies

MAGI2-AS3 has been decreased in prostate cancer cells. Up-regulation of MAGI2-AS3 in LNCaP and PC3 cells has inhibited proliferation ability, migration aptitude, and invasion of these cells. This lncRNA has been shown to target miR-142-3p in these cells [27]. Another study in prostate cancer has revealed that up-regulation of MAGI2-AS3 decreases cell viability and induces apoptosis in PC-3 and DU145 cells. Moreover, up-regulation of MAGI2-AS3 decreases STAT3 activity in mentioned cell lines. miR-424-5p, an inducer of STAT3 pathway, has been shown to be targeted by MAGI2-AS3 (Fig. 2). In fact,

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MAGI2-AS3 affects expression of miR-424-5p and its target mRNA COP1 in mentioned prostate cancer cell lines. IL-6-associated stimulation of STAT3 pathway can decrease the impact of MAGI2-AS3 in these cells [36].

Up-regulation of MAGI2-AS3 in clear cell renal cell carcinoma cells has reduced viability and migration of these cells. Moreover, up-regulation of MAGI2-AS3 has inhibited vessel-like tube formation of HUVECs. Mechanistically, MAGI2-AS3 binds with HEY1 and decreases enrichment of HEY1 at the ACY1 promoter leading to up-regulation of ACY1 expression. Taken together, MAGI2-AS3 has tumor suppressor role and anti-angiogenic activities in this type of carcinoma through modulation of HEY1/ACY1 pathway [35].

Conversely, MAGI2-AS3 has been found to have a tumor-promoting role in pancreatic cancer cells promoting viability, migratory aptitude and invasion of these cells. miR-490-5p which targets this lncRNA has anti-cancer effect in these cells influencing epithelial-mesenchymal transition (EMT) [39].

In cervical cancer cells, up-regulation of MAGI2-AS3 has suppressed proliferative and invasive capacity of cells through influencing expression of miR-15b and subsequently affecting levels of its target mRNA CCNE1 [3]. Regulation of activity of miR-233/EPB41L3 axis is another identified mechanism for anti-cancer effects of MAGI2-AS3 in SiHa and HeLa [23]. On the other hand, MAGI2-AS3 has been reported to induce oncogenic roles in C-33A via up-regulation of CDK6 [25].

In acute lymphoblastic leukemia cells, MAGI2-AS3 has anti-proliferative and pro-apoptotic effects through modulating miR-452-5p/FOXN3 molecular route [39]. Moreover, it can inhibit glycolysis in these cells [39]. Besides, MAGI2-AS3 can constrains self-renewal ability of leukaemic stem cells through enhancing TET2-related DNA demethylation of the LRIG1 promoter in these cells [5]. Table 1 summarizes the effects of MAGI2-AS3 in different cancer cell lines.

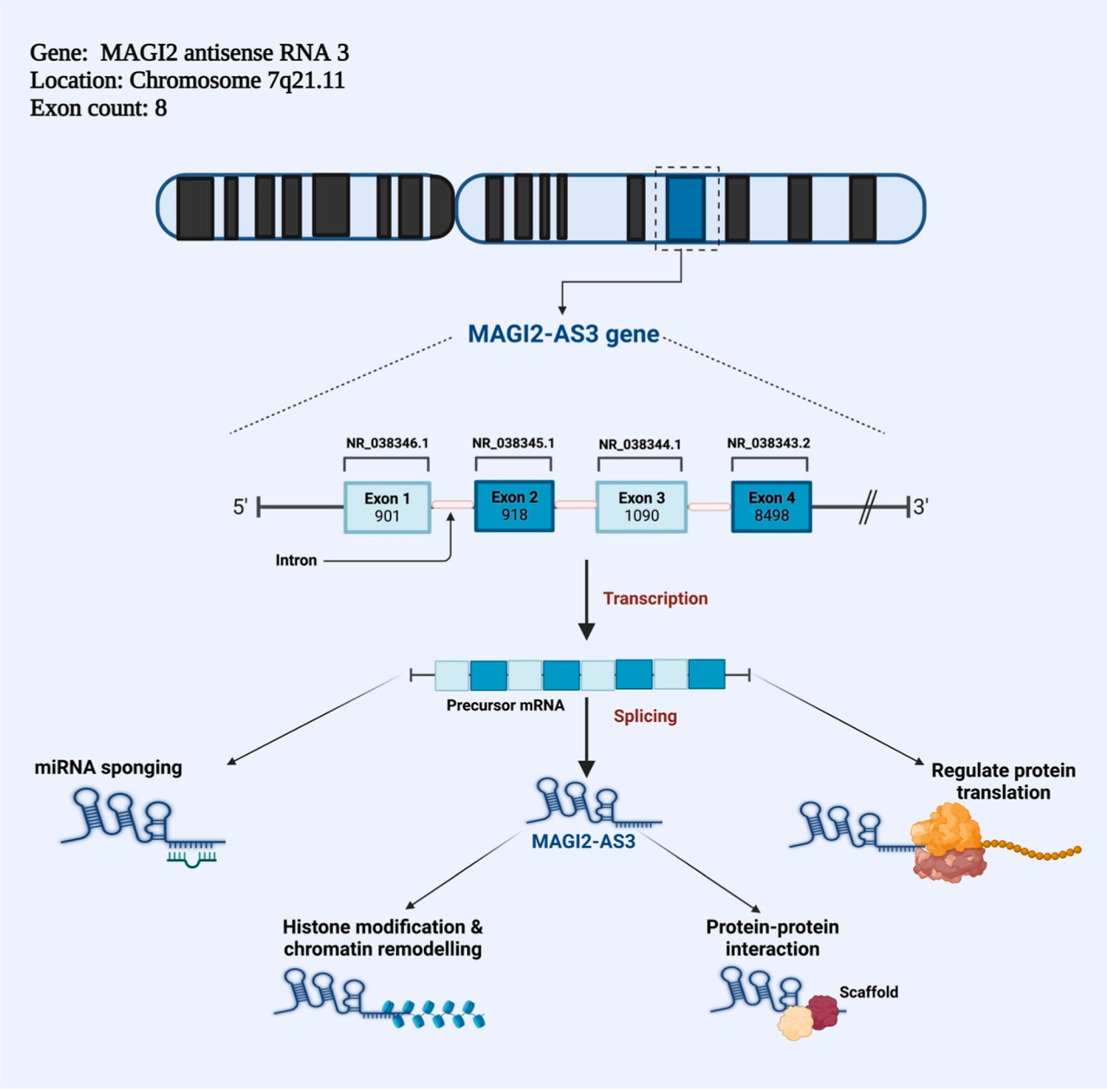

Fig. 1. The structure and location of the lncRNA MAGI2-AS3 gene. After the splicing process, the mature lncRNA MAGI2-AS3 is created. This lncRNA has many roles, including protein-protein interactions, histone modifications, miRNA sponges, and regulation of the translation process.

2.2. Animal studies

Experimentations in xenograft models of different cancers are principally in favor of anti-tumor role of MAGI2-AS3 (Table 2) except for two studies in mice models of nasopharyngeal carcinoma [2] and colorectal cancer [29] which support an oncogenic role for this lncRNA. Besides, in nasopharyngeal carcinoma models, MAGI2-AS3 down-regulation has reduced resistance to cisplatin [2]. Therefore, this lncRNA can be regarded as a target for reduction of chemoresistance. Most importantly, an experiment in BALB/c nude mice model of acute myeloid leukemia has confirmed the role of MAGI2-AS3 in suppression of self-renewal capacity of leukemic stem cells [5].

2.3. Assays in clinical specimens

MAGI2-AS3 has been decreased while expression of miR-142-3p has been increased in sera of prostate cancer patients [24]. Moreover, expression levels of MAGI2-AS3 in prostate cancer samples have been inversely correlated with miR-424-5p levels, while positively correlated with COP1 levels [36]. MAGI2-AS3 and ACY1 expressions have been found to be downregulated in clear cell renal carcinoma samples, and down-regulation of MAGI2-AS3 has been associated with poor patient survival [35]. Similarly, expression of MAGI2-AS3 has been downregulated, while miR-15b levels have been upregulated in cervical cancer samples. More importantly, down-regulation of MAGI2-AS3 in cervical cancer patients has been associated with poor prognosis [3].

In brief, most of expression assays in clinical samples support down-regulation of MAGI2-AS3 in malignant tissues compared with their non-malignant tissues (Table 3). Exceptions to this finding have been observed in lung squamous cell carcinoma [32], pancreatic cancer [39], cervical cancer [25], and gastric cancer [4]. It is worth mentioning that other studies in lung [48] and cervical [3] cancers are in favor of the tumor suppressor role of this lncRNA.

Association between MAGI2-AS3 expression and clinicopathological data has been verified in different cancers. Most importantly, in breast cancer samples, expression levels of MAGI2-AS3 have been negatively associated with grade, TNM stage, hormone receptors expression, and Her-2 expression [42].

A large scale association study in patients with colorectal cancer and age- and gender-matched cancer-free control subjects has shown that GG genotype of rs7783388 within MAGI2-AS3 confers a higher risk of colorectal cancer compared with other genotypes. Mechanistical studies have shown that rs7783388 A > G decreases binding affinity of glucocorticoid receptor to the promoter region of MAGI2-AS3, leading to lower transcriptional activity of its promoter [41].

ROC curve analyses have shown serum levels of MAGI2-AS3 can

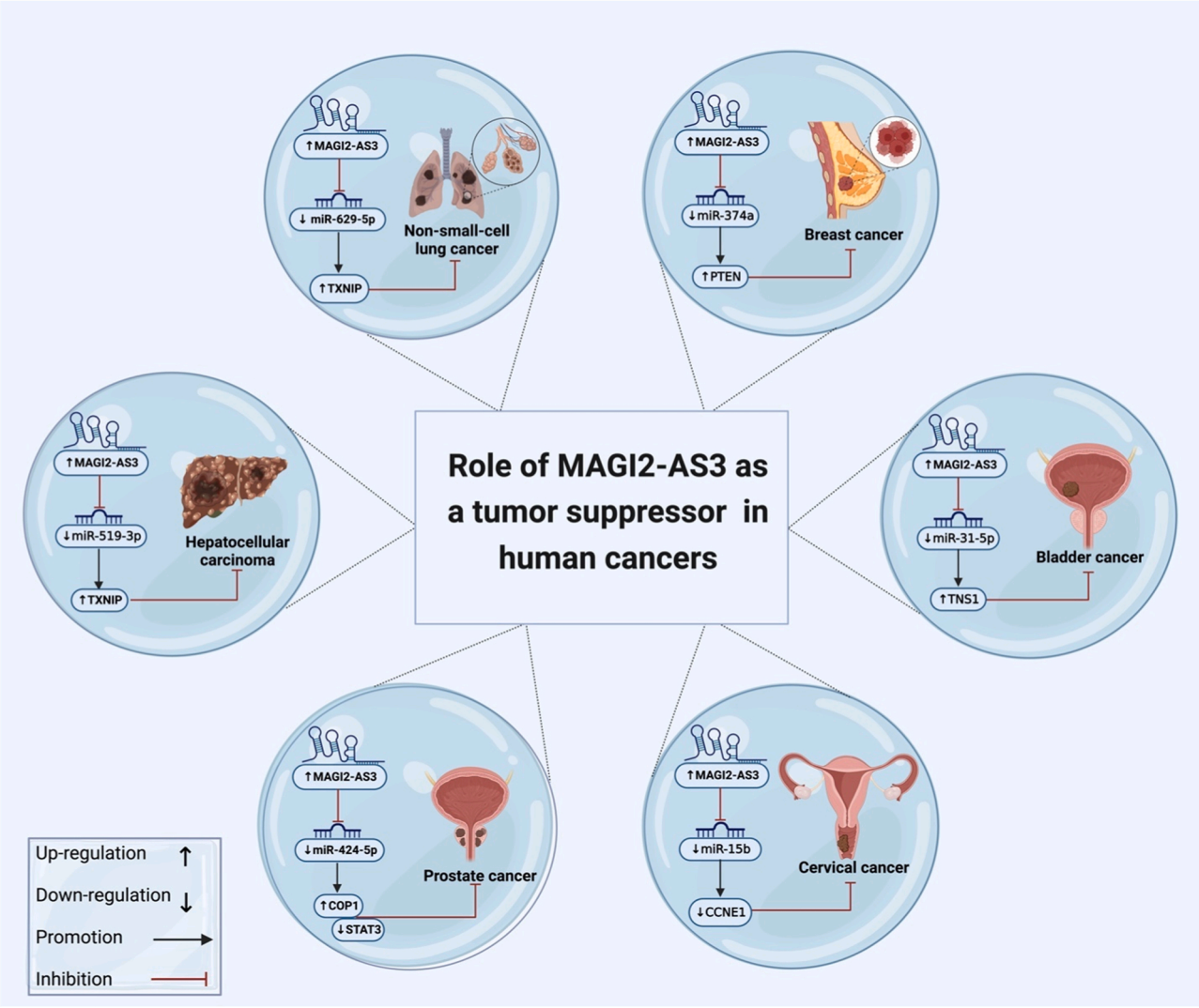

Fig. 2. Alteration of MAGI2-AS3 expression and related signaling pathways in different types of cancer such as, breast, lung, liver, cervical, prostate and bladder cancers.

Table 1
Expression pattern of MAGI2-AS3 in cancer cell lines (**Δ**: knock-down or deletion, ↑: overexpression, →: results in, EMT: Epithelial-mesenchymal transition, LSC: leukemia stem cell).

Tumor type	Targets/ Regulators	Cells	Function	Refs.
Prostate cancer	miR-142-3p	PC-3 and LNCaP	↑ MAGI2-AS3 (which sponges miR-142-3p): ↓ proliferation ↓ migration ↓ invasion	[24]
	miR-424-5p/COP1/ STAT3	PC-3 and DU145	↑ MAGI2-AS3→ ↓ miR-424-5p: ↑ COP1 ↓ STAT3: ↓ proliferation ↑ apoptosis	[36]
Clear cell renal cell carcinoma	HEY1/ACY1	786-O, KCC-853, RCC-9863, RLC-310 and Caki1	↑ MAGI2-AS3→ ↓ HEY1→ ↑ ACY1: ↓ viability ↓ migration ↓ invasion ↓ EMT	[35]
Pancreatic cancer	miR-490-5p	PANC-1, SW1990, AsPC-1 and BxPC-3	↑ miR-490-5p→ ↓ MAGI2-AS3: ↓ proliferation ↓ migration ↓ invasion ↓ EMT ↑ apoptosis	[39]
Cervical cancer	miR-15b/ CCNE1	HeLa, SiHa, and CaSki	↑ MAGI2-AS3 (which sponges miR-15b): → ↓ CCNE1: ↓ proliferation ↓ invasion	[3]
	miR-233/ EPB41L3	SiHa and HeLa	↑ MAGI2-AS3 (which sponges miR-233) → ↑ EPB41L3: ↓ invasion ↓ migration	[23]
	CDK6	C-33A	↓ MAGI2-AS3 → ↓ CDK6: ↓ proliferation	[25]
Acute lymphoblastic leukemia	miR-452-5p/FOXN3	Jurkat and Reh	↑ MAGI2-AS3 (which sponges miR-452-5p): → ↑ FOXN3: ↓ proliferation ↓ glycolysis ↑ apoptosis	[39]
Acute myeloid leukemia	TET2/LRIG1	LSCs	↑ MAGI2-AS3 (which recruits TET2 to the promoter region of LRIG1) → ↑ demethylation of LRIG1 → ↑ LRIG1: ↓ self-renewal of LSCs	[5]
Non-small-cell lung cancer	miR-629-5p/TXNIP	Beas-2B, A549, and H1299	↑ MAGI2-AS3→ ↓ miR-629-5p → ↑ TXNIP: ↓ proliferation ↓ invasion	[19]
	miR-25/ RECK	H1993	↑ MAGI2-AS3 (which sponges miR-25) → ↑ RECK: ↓ migration ↓ invasion	[31]
	miR-155/ SOCS-1	H23	↑ MAGI2-AS3 (which sponges miR-155) → ↑ SOCS-1: ↓ proliferation	[1]
	miR-23a-3p/ PTEN	A549, PC9, NCI-H441, and NCI-H1650	↑ MAGI2-AS3 (which sponges miR-23a-3p) → ↑ PTEN: ↓ proliferation ↓ invasion	[21]
Hepatocellular carcinoma	miR-519c-3p/TXNIP	Huh7, Hep3B, SNU-182	↑ MAGI2-AS3 (which sponges miR-519-3p): ↑ TXNIP: ↓ proliferation ↑ apoptosis	[22]
	miR-23a-3p/ PTEN	Bel-7402, Huh-7, HepG2, and SMMC-7721	↑ MAGI2-AS3 (which sponges miRNA-23a-3p): ↑ PTEN: ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis	[19]
	ROCK2	Hep3B and MHCC97-H	↑ MAGI2-AS3 → ↓ROCK2: ↓ invasion ↓ migration	[12]
	KDM1A/ RACGAP1	HuH-7, HCCLM3, HepG2, BEL-7402, SK-HEP-1, and SMMC-7721	↑ MAGI2-AS3 (which recruits KDM1A to the promoter of RACGAP1) → demethylation of RACGAPP1 → ↓ RACGAP1: ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis	[28]
	miR-374b-5p/SMG1	HepG2, Hep3B, and MHCC-97 H	↑ MAGI2-AS3 (which sponges miR-374b-5p) → ↑ SMG1: ↓ proliferation ↓ migration ↓ viability ↑ cell cycle arrest ↑ apoptosis	[43]
Breast cancer	MAGI2/ AKT/Wnt	MCF-7	↑ MAGI2-AS3→ ↑ MAGI2 ↓ AKT/Wnt: ↓ proliferation ↓ migration	[38]
	miR-374a/ PTEN	MDA-MB-231 and MCF-7	↑ MAGI2-AS3 (which sponges miR-374a) → ↑ PTEN: ↓ migration ↓ invasion	[11]
	Fas/FasL	MDA-MB-231 and MCF-7	↑ MAGI2-AS3 → ↑ Fas/FasL: ↓ viability ↓ colony formation ↑ apoptosis	[42]
Bladder cancer	MAGI2/ PTEN	T24, J82, 5637 and RT4	↑ MAGI2-AS3→ ↑ MAGI2 & PTEN: ↓ migration ↓ invasion ↓ EMT	[10]
	miR-31-5p/ TNS1	T24 and J82	↑ MAGI2-AS3 (which sponges miR-31-5p) → ↑ TNS1: ↓ proliferation	[33]

(*continued on next page*)

Table 1 (*continued*)

Tumor type	Targets/ Regulators	Cells	Function	Refs.
			↓ migration ↓ invasion	
	miR-15b-5p/CCDC19	EJ, T24 and RT4	↑ MAGI2-AS3 (which sponges miR-15b-5p) → ↑ CCDC19: ↓ proliferation ↓ migration ↓ invasion ↓ colony formation	[13]
Esophageal cancer	EZH2/ HOXB7	KYSE30, KYSE150 and KYSE450	↑ MAGI2-AS3 (which recruits EZH2 to the promoter region of HOXB7) → ↓ HOXB7: ↓ proliferation ↑ apoptosis ↑ radiosensitivity	[7]
Colorectal cancer	-	RKO, SW480, and SW620	↑ MAGI2-AS3: ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis	[41]
	miR-3163/ TMEM106B	HCT-116, RKO, SW480, and HT-29	Δ MAGI2-AS3 (which sponges miR-3163) → ↑ miR-3163 → ↓ TMEM106B: ↓ proliferation ↓ migration ↑ apoptosis	[29]
Ovarian cancer	miR-525-5p/MXD1/ MYC	SKOV3, SNU119, OVCAR-3, SUN8, Caov3	↑ MAGI2-AS3 (which sponges miR-525-5p) → ↑ MXD1 & ↓ MYC: ↓ proliferation ↓ migration ↓ invasion ↑ apoptosis ↑ cell cycle arrest	[4]
High-Grade Serous Ovarian Carcinoma	miR-15-5p/ miR-374a-5p/miR-374b-5p	PEA1 and KURAMOCHI	↑ MAGI2-AS3 (which sponges miR-15-5p/miR-374a-5p/miR-374b-5p): ↓ migration ↓ viability	[18]
Nasopharyngeal carcinoma	miR-218-5p/GDPD5/ SEC61A1	CNE1, SUNE1, HNE1, and 5-8F	Δ MAGI2AS3→ ↑ miR-218-5p → ↓ GDPD5: ↓ proliferation ↓ migration ↓ EMT ↓ resistance to cisplatin	[2]
Gastric cancer	BRD4/miR-141-3p & miR-200a-3p/ZEB1	MKN74, MKN45, KATO III, AGS, and HGC27	Δ BRD4 → ↓ MAGI2-AS3 Δ MAGI2-AS3 (which sponges miR-141-3p & miR-200a-3p) → ↑ miR-141-3p and miR-200a-3p → ↓ ZEB1: ↓ migration ↓ invasion	[4]
Lung squamous cell carcinoma	miR-374a-5p/miR-374b-5p/ CADM2	H2170, H226, SW900, SK-MES-1	↑ MAGI2-AS3 (which sponges miR-374a-5p & miR-374b-5p) → ↑ CADM2: ↓ proliferation ↓ migration	[48]

Table 1 (*continued*)

Tumor type	Targets/ Regulators	Cells	Function	Refs.
			↓ invasion ↑ apoptosis	

Table 2
MAGI2-AS3 effect in carcinogenesis as seen in animal models of cancer (Δ: knock-down or deletion, LSC: leukemia stem cell, SPF: specific pathogen-free).

Tumor type	Animal models	Results	Refs.
Clear cell renal cell carcinoma	BALB/c-nu/nu mice	↑ MAGI2-AS3: ↓ tumor growth ↓ angiogenesis	[35]
Acute lymphoblastic leukemia	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor growth	[39]
Acute myeloid leukemia	NOD/SCID mice	↑ MAGI2-AS3: ↓ self-renewal of LSCs ↑ survival rate	[5]
Non-small-cell lung cancer	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor growth	[19]
Hepatocellular carcinoma	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor growth	[22]
	SPF nude mice	↑ MAGI2-AS3: ↓ tumor growth	[28]
	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor growth	[43]
Bladder cancer	NOD/SCID mice	↑ MAGI2-AS3: ↓ metastasis	[10]
	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor volume and weight	[13]
Esophageal cancer	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor growth	[7]
Nasopharyngeal carcinoma	BALB/c male mice	Δ MAGI2-AS3: ↓ tumor growth ↓ resistance to cisplatin	[2]
Colorectal cancer	BALB/c nude mice	Δ MAGI2-AS3: ↓ tumor growth	[29]
Lung squamous cell carcinoma	BALB/c nude mice	↑ MAGI2-AS3: ↓ tumor growth ↓ metastasis	[48]

separate prostate cancer patients from healthy subjects with AUC, sensitivity and specificity values of 0.953, 91.5 % and 84.7 %, respectively [24]. Other studies in serum or plasma samples of patients affected with diverse types of cancers have reported promising results for application of MAGI2-AS3 transcript levels as a diagnostic marker (Table 4). Moreover, an in silico analysis of TCGA datasets of paired breast cancer and adjacent non-cancerous tissues has shown high accuracy of MAGI2-AS3 levels for separation of these two sets of tissues [47].

2.4. Non-malignant disorders

Congenital diaphragmatic hernia, Alzheimer's disease and intervertebral disc degeneration are three disorders that are possibly associated with dysregulation of MAGI2-AS3. Mechanistical studies have been performed to identify the role of this lncRNA in two of these disorders (Table 5).

Plasma levels of MAGI2-AS3 have been found to be lower in intervertebral disc degeneration patients compared with controls. Moreover, expression levels of MAGI2-AS3 could effectively distinguish these patients from healthy controls. Most notably, plasma levels of this lncRNA have been elevated after treatment of patients. Mechanistically, upregulation of MAGI2-AS3 inhibits FasL expression in nucleus pulposus cells. Thus, MAGI2-AS3 has a role in the regulation of FasL expression in these cells [8]. Dysregulation of MAGI2-AS3 levels can alos participate in the pathogenesis of Alzheimer's disease, since this lncRNA has a role

Table 3
Abnormal levels of MAGI2-AS3 in clinical specimens (ANT: adjacent normal tissue, OS: overall survival, DFS: disease-free survival, RFS: relapse-free survival, BM: bone marrow, ER: Estrogen receptor, PR: progesterone receptor).

Malignancy	Samples	Expression (tumor versus normal)	Kaplan-Meier Analysis (Impact of MAGI2-AS3 dysregulation)	Univariate/ Multivariate cox regression	Association of MAGI2-AS3 expression with clinical characteristics	Refs.
Acute myeloid leukemia (AML)	41 ALL BM + 12 healthy controls BM + GSE17054 dataset	Downregulated	-	-	-	[5]
Lung squamous cell carcinoma (LUSC)	TCGA dataset + GSE29013, GSE30219, GSE37745 and GSE50081 datasets	Upregulated	-	-	-	[32]
	41 LUSC + paired ANT	Downregulated	Shorter OS	-	-	[48]
Clear cell renal cell carcinoma (ccRCC)	86 ccRCC + paired ANT	Downregulated	Shorter OS	-	Associated with TNM stage, Fuhrman grade, and tumor size	[35]
Pancreatic cancer (PC)	20 PC + paired ANT	Upregulated	-	-	-	[39]
Cervical cancer (CC)/cervical squamous cell carcinoma (CSCC)	47 CC + paired ANT	Downregulated	Shorter OS	-	-	[3]
	60 CSCC + paired ANT	Downregulated	-	-	Associated with tumor diameter, HPV types and stages	[23]
	64 CSCC + paired ANT	Upregulated	Shorter OS	-	-	[25]
Acute lymphoblastic leukemia (ALL)	25 ALL BM + 25 healthy controls BM	Downregulated	-	-	-	[39]
Prostate cancer (PCa)	109 PCa + paired ANT + GSE46602 and GSE55945 datasets + TCGA dataset	Downregulated	-	-	Associated with high Gleason score	[36]
	TCGA dataset, GSE17951, and GSE7076	Downregulated	-	-	-	[1]
Non-small-cell lung cancer (NSCLC)	GSE51852, GSE52248, and GSE81089 datasets	Downregulated	Shorter OS	-	-	[19]
	96 NSCLC + paired ANT	Downregulated	-	-	-	[30]
	78 NSCLC + paired ANT	Downregulated	-	-	-	[31]
	62 NSCLC + paired ANT	Downregulated	Shorter OS	-	-	[1]
	40 NSCLC + paired ANT	Downregulated	Shorter OS	-	-	[21]
	Plasma and platelets of 68 adenocarcinomas + 33 squamous cell carcinomas, + 60 healthy controls, GSE19188, GSE30219, and GSE27262 datasets	Downregulated in adenocarcinomas and squamous cell carcinomas	-	-	Associated with TNM stage, lymph node metastasis and distant metastasis	[26]
Ovarian cancer (OV)	GSE54388 and GSE74448 datasets + GEPIA	Downregulated	-	-	-	[37]
Hepatocellular carcinoma (HCC)	27 HCC + paired ANT	Downregulated	-	-	-	[22]
	40 HCC + paired ANT	Downregulated	Shorter OS	-	Associated with tumor size, TNM stage, and metastasis	[19]
	68 HCC serum + 68 healthy controls serum	Downregulated	-	-	-	[12]
	58 HCC + 20 healthy controls + GEPIA + GSE45267, GSE49515 and GSE62232 datasets	Downregulated	Shorter OS	-	Associated with tumor size, clinical stage, and lymph node metastasis	[28]
	88 HCC + paired ANT	Downregulated	Shorter OS	Independent prognostic marker for HCC	Associated with tumor size, lymph node metastasis and TNM stage	[43]
Breast cancer (BC)	24 BC + paired ANT + TCGA dataset	Downregulated	Shorter OS	-	-	[38]
	TCGA dataset + GSE125677 + GEPIA	Downregulated	Shorter OS	-	Associated with lymph node metastasis	[47]
	30 BC + paired ANT	Downregulated	-	-	Negatively associated with histological grade, TNM stage, expression of ER, PR and Her-2	[42]
Triple negative breast cancer (TNBC)	GSE60689 and GSE64790 datasets	Downregulated	Poor RFS	-	-	[34]
Bladder cancer (BCa)	80 BCa + 30 paired ANT	Downregulated	Shorter OS	-	Associated with tumor stage, number of tumors, tumor grade	[10]
	45 BCa + paired ANT + TCGA dataset	Downregulated	-	-	-	[33]
	58 BCa + paired ANT + TCGA dataset	Downregulated	Shorter OS	-	-	[13]
Esophageal cancer (EC)	92 EC + paired ANT + GSE45670 + GEPIA	Downregulated	-	-	-	[7]
Colorectal cancer (CRC)	200 CRC + paired ANT	Downregulated	-	-	-	[41]

(*continued on next page*)

Table 3 (*continued*)

Malignancy	Samples	Expression (tumor versus normal)	Kaplan-Meier Analysis (Impact of MAGI2-AS3 dysregulation)	Univariate/ Multivariate cox regression	Association of MAGI2-AS3 expression with clinical characteristics	Refs.
Gastric cancer (GC)	TCGA dataset + GSE54129, GSE62254 and GSE79973 datasets	Upregulated	Shorter OS/ shorter DFS	Independent prognostic factor for OS and DFS	-	[4]
	18 GC + paired ANT + TCGA dataset + GSE53137, GSE95667, and GSE111762 datasets	Downregulated in early stages compared to advanced stages (without statistical significance in 18 GC tissues)	Better OS in downregulated samples	Independent prognostic factor with OS	Associated with lymph node metastasis	[45]
Glioma	178 glioma tissues + paired ANT	Downregulated	Shorter OS	Independent prognostic factor with OS, WHO grade and KPS score	Associated with WHO grade and KPS score	[6]

Table 4
Diagnostic value of MAGI2-AS3 in diseases.

Disease type	Samples	Distinguish between	Area under curve	Sensitivity (%)	Specificity (%)	Refs.
Prostate cancer (PCa)	Serum of PCa patients	Patient vs. healthy	0.953	91.5	84.7	[24]
Hepatocellular carcinoma (HCC)	68 HCC serum + 68 healthy controls serum	Patient vs. healthy	0.9138	-	-	[12]
Intervertebral disc degeneration (IDD)	66 IDD plasma + 58 healthy controls plasma	Patient vs. healthy	0.90	-	-	[8]
Breast cancer	TCGA dataset + GSE125677 + GEPIA	Cancerous vs. non-cancerous tissues	0.985	-	-	[47]
Non-small-cell lung cancer	Plasma and platelets of 68 adenocarcinomas (AD) + 33 squamous cell carcinomas (SCC) + 60 healthy controls	Patient vs. healthy	0.853 in platelets of AD + 0.866 in plasma of AD	-	-	[26]
			0.892 in platelets of SCC + 0.887 in plasma of SCC	-	-	[26]

Table 5
Cell line studies on the role of MAGI2-AS3 in non-malignant conditions (Δ: knock-down or deletion, NP: nucleus pulposus).

Disease type	Interactions	Cell line	Function	Refs.
Alzheimer's disease	miR-374b-5p	SH-SY5Y and BV2	↓ MAGI2-AS3→ ↑ miR-374b-5p: ↑ viability ↓ inflammation	[44]
Intervertebral disc degeneration (IDD)	FasL	NP cells	↑ MAGI2-AS3 → ↓ FasL	[8]

in the regulation of amyloid-β associated neurotoxicity and neuro-inflammation through sequestering miR-374b-5p [44] (Fig. 3). Finally, a comprehensive gene profiling experiment in congenital diaphragmatic hernia has revealed up-regulation of MAGI2-AS3 in this context (Table 6).

3. Discussion

MAGI2-AS3 can act as oncogene or tumor suppressor via modulation of multiple cancer-related signaling pathways. MAGI2-AS3 can also serve as a molecular sponge for miR-142-3p, miR-15b, miR-233, miR-452-5p, miR-629-5p, miR-25, miR-155, miR-23a-3p, miR-519c-3p, miR-374b-5p, miR-374a, miR-31-5p, miR-3163, miR-525-5p, miR-15-5p, miR-374a-5p, miR-374b-5p, miR-218-5p, miR-141-3p and miR-200a-3p to regulate expression of their mRNA targets. Several pathways including miR-23a-3p/PTEN, AKT/Wnt, Fas/FasL, and miR-3163/TMEM106B have been shown to mediate the effects of MAGI2-AS3 in the carcinogenesis.

Several studies have revealed association between expression of MAGI2-AS3 and clinical features of malignancies as well as outcome of patients, emphasizing on the role of this lncRNA as a prognostic marker. Moreover, detection of MAGI2-AS3 expression in biofluids has suggested its possible application as a diagnostic marker.

An unexplored area in research about this lncRNA is association between genetic variants within or near *MAGI2-AS3* coding gene and risk of cancers. This information would facilitate prediction of risk of different cancers.

Among non-malignant conditions, congenital diaphragmatic hernia, Alzheimer's disease and intervertebral disc degeneration are disorders that are possibly associated with dysregulation of MAGI2-AS3. The mechanisms of involvement of this lncRNA in these conditions are less studied. However, miR-374b-5p and FasL have been found to mediate the effects of MAGI2-AS3 in this regard.

Taken together, MAGI2-AS3 is a putative diagnostic and prognostic marker in cancers. The application of this lncRNA as a diagnostic marker has been studied in prostate cancer, hepatocellular carcinoma, breast cancer and non-small-cell lung cancer. However, the impact of MAGI2-AS3-targeted therapies on the progression of tumors has not fully assessed. This field is being complicated by the dual roles of MAGI2-AS3 in the carcinogenesis.

CRediT authorship contribution statement

SGF wrote the draft and revised it. MT designed and supervised the study. FR, BMH and AA collected the data and designed the figures and

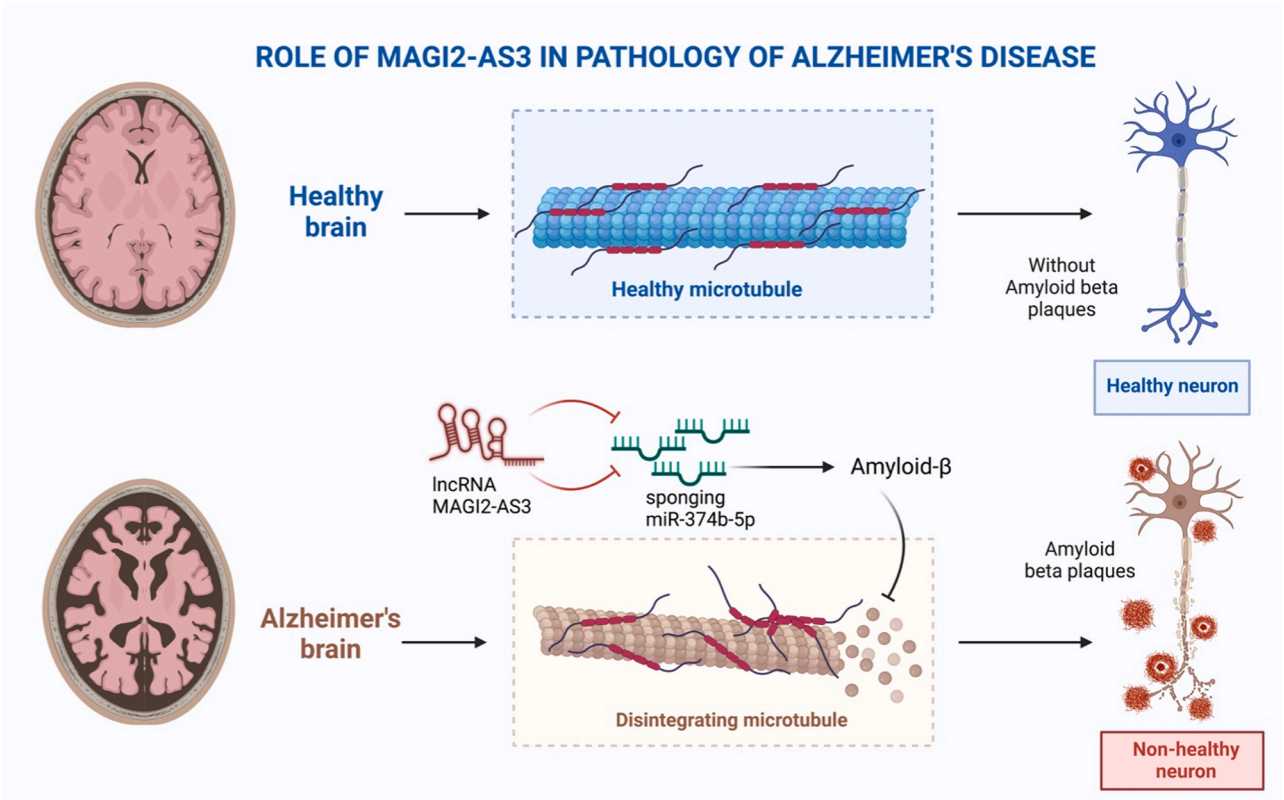

Fig. 3. Functional role of lncRNA MAGI2-AS-3 in patients with Alzheimer's disease. By sponging miR-374b-5p, MAGI2-AS3 affects the neurotoxicity and neuro-inflammation caused by amyloid-β in Alzheimer's disease.

Table 6
Summary of human studies on the role of MAGI2-AS3 in non-malignant conditions.

Disease	Number of samples	Expression (case vs. control)	Association	Method	Refs.
Congenital diaphragmatic hernia (CDH)	9 CDH + 1 healthy control	Upregulated	Associated with diaphragm	High throughput sequencing, qRT-PCR	[20]
Alzheimer's disease (AD)	48 AD serum + 30 healthy controls serum	Upregulated	Severity of disease	qRT-PCR	[44]
Intervertebral disc degeneration (IDD)	66 IDD plasma + 58 healthy controls plasma	Downregulated	-	qRT-PCR	[8]

tables. All the authors read the submitted version and approved it.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Availability of Data and Materials

Not applicable.

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